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| Martin Moynihn<br>Prtsi Inc<br>PO Box 16446<br>Arlington, VA 22215 |             |                      | EXAMINER<br>RAMIREZ, DELIA M |                        |
|  |             |                      | ART UNIT<br>1652             | PAPER NUMBER           |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

## Application No.

10/554,387

## Applicant(s)

SHAALTIEL ET AL.

## Examiner

Delia M. Ramirez

## Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 07 May 2008.  
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☐ Claim(s) 73-144 is/are pending in the application.  
4a) Of the above claim(s) 73-97, 103, 121 and 129-141 is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 98-102, 104-120, 122-128 and 142-144 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.  
10) ☒ The drawing(s) filed on 25 October 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☒ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Final Drawing Review (PTO-849)  
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 1/18/07, 5/7/08  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_  
5) ☐ Notice of Informal Patent Application  
6) ☒ Other: alignments

## **DETAILED ACTION**

### ***Status of the Application***

Claims 73-144 are pending.

Applicant's preliminary amendment adding new claims 142-144 as submitted in a communication filed on 5/7/2008 is acknowledged.

Applicant's election of Group III, claims 99-102, 104-120, 122-128, drawn in part to a glucocerebrosidase and compositions thereof, as submitted in a communication filed on 5/7/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

New claims 142-144 are deemed directed to the elected subject matter. Claims 73-97, 103, 121, 129-141 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Linking claim 98 is not deemed allowable at this time, thus the restriction requirement can be properly maintained. Claims 98-102, 104-120, 122-128, 142-144 are at issue and are being examined herein.

### ***Specification***

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title refers to a process. It is suggested the title be amended to refer to the elected polypeptide. Appropriate correction is required.
2. The specification is objected for not complying with sequence rules. See page 31, lines 4-6, 24-25, and page 32, line 3. Applicant is required to insert sequence identifiers in front of sequences referred to in the specification. See particularly 37 CFR 1.821(d). Applicant is requested to make the appropriate changes.

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3. The specification is objected to for the following reasons. An alignment of SEQ ID NO: 8 against the known human glucocerebrosidase sequence shows that the polypeptide of SEQ ID NO: 8 is missing a significant portion of the human glucocerebrosidase (162 amino acids corresponding to amino acids 153-314 of GLCM\_HUMAN. See attached alignment. It is unclear to the examiner if the polypeptide of SEQ ID NO: 8 has enzymatic activity in view of the significant portion of the known glucocerebrosidase missing. The specification does not provide any information as to how the polypeptide of SEQ ID NO: 8 is different from the known human glucocerebrosidase. Clarification is required.

***Priority***

4. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to ISRAEL 155588 filed on 04/27/2003. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The certified copy of the foreign priority document is in English.
5. This application is the US national stage of PCT/IL04/00181 filed on 02/24/2004.

***Information Disclosure Statement***

6. The information disclosure statements (IDS) submitted on 1/18/2007 and 5/7/2008 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

***Drawings***

7. The drawings submitted on 10/25/2005 are objected to for the following reasons. The reproduction of the photograph shown in Figure 3C is of poor quality. Thus, the Examiner is unable to determine what is shown in this figure. Appropriate correction is required.

***Claim Objections***

8. Claims 104, 105, 106, 107, 122, 123, 124, 142 are objected to due to the recitation of "vacuolar targeting signal". It should be amended to recite "vacuolar targeting signal peptide". Appropriate correction is required.

9. Claims 104 and 122 are objected to due to the recitation of "wherein said human lysosomal protein is contiguously linked to a C-terminal vacuolar targeting signal". The term as recited may be interpreted as indicating that the human lysosomal protein is contiguously linked to the C-terminus of a vacuolar targeting signal. To clearly indicate that the targeting signal is at the C-terminus of the human lysosomal protein recited, it is suggested the term be amended to recite, for example, "wherein said human lysosomal protein is linked at its C-terminus to a vacuolar targeting signal peptide". Appropriate correction is required.

10. Claims 105 and 123 are objected to due to the recitation of "wherein said human lysosomal protein is contiguously linked to a C-terminal vacuolar targeting signal and an N-terminal endoplasmic reticulum signal peptide". The term as recited may be interpreted as indicating that the human lysosomal protein is contiguously linked to the C-terminus of a vacuolar targeting signal and the N-terminus of an endoplasmic reticulum signal peptide. To clearly indicate that the targeting signal is at the C-terminus of the human lysosomal protein recited and the endoplasmic reticulum signal peptide is at the N-terminus of the human lysosomal protein recited, it is suggested the term be amended to recite, for example, "wherein

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said human lysosomal protein is linked at its C-terminus to a vacuolar targeting signal peptide and at its N-terminus to an endoplasmic reticulum signal peptide". Appropriate correction is required.

11. Claims 107, 108, 125 and 126 are objected to due to the recitation of "wherein said ... signal ... is as set forth in SEQ ID NO: 2/1". To enhance clarity and to be consistent with commonly used claim language, it is suggested the term be amended to recite, for example, "wherein said vacuolar targeting signal peptide/endoplasmic reticulum signal peptide comprises/consists of SEQ ID NO: 2/1".

Appropriate correction is required.

12. Claim 109 is objected to due to the recitation of "wherein said human glucocerebrosidase comprises an amino acid sequence as set forth in SEQ ID NO: 8". To be consistent with commonly used claim language, it is suggested the term be amended to recite, for example, "wherein said human glucocerebrosidase comprises the amino acid sequence as set forth in SEQ ID NO: 8". Appropriate correction is required.

13. Claim 110 is objected to due to the recitation of "wherein said lysosomal protein having a biological activity". It is suggested the term be amended to recite "wherein said lysosomal protein has a biological activity". Appropriate correction is required.

14. Claim 113 is objected to due to the recitation of "protein of claim 11, having an increased affinity...". It is suggested the term be amended to recite, for example, "protein of claim 11, wherein said protein has an increased...". Appropriate correction is required.

15. Claim 120 is objected to due to the recitation of "protein comprises an amino acid sequence as set forth in SEQ ID NO: 8". To be consistent with commonly used claim language, it is suggested the term be amended to recite, for example, "protein comprises the amino acid sequence as set forth in SEQ ID NO: 8". Appropriate correction is required.

16. Claim 142 is objected to due to the recitation of "human glucocerebrosidase which comprises an amino acid sequence as set forth in SEQ ID NO: 8 contiguously linked to a C-terminal vacuolar

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targeting signal as set forth in SEQ ID NO: 2 and an N-terminal endoplasmic reticulum signal peptide as set forth in SEQ ID NO: 1". To clearly indicate the location of the signal peptides and to be consistent with commonly used claim language, it is suggested the term be amended to recite, for example, "human glucocerebrosidase which comprises the amino acid sequence as set forth in SEQ ID NO: 8, wherein said human glucocerebrosidase is linked at its C-terminus to the vacuolar targeting signal peptide of SEQ ID NO: 2, and at its N-terminus to the endoplasmic reticulum signal peptide of SEQ ID NO: 1".

Appropriate correction is required.

17. Claim 143 is objected to due to the recitation of "protein of claim 142, which comprises an amino acid sequence as set forth in SEQ ID NO: 14". To enhance clarity and to be consistent with commonly used claim language, it is suggested the term be amended to recite "protein of claim 142 wherein said protein comprises the amino acid of SEQ ID NO: 14". Appropriate correction is required.

***Claim Rejections - 35 USC § 112, Second Paragraph***

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 110-113, 127 and 143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. Claim 110 is indefinite in the recitation of "protein having a biological activity" because it is unclear how it further limits claim 98. The term "biological activity" can have many different interpretations to one of skill in the art. For example, one interpretation of the term "biological activity" in regard to polypeptides is the ability to elicit antibodies. It is suggested that the term be replaced with a term which clearly defines Applicant's intended biological activity. For examination purposes, claim 110 will be considered a duplicate of claim 98. Correction is required.

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21. Claim 111 is indefinite in the recitation of “protein of claim 98, wherein said biological activity is uptake into macrophages” for the following reasons. There is no antecedent basis for a biological activity in claim 98. For examination purposes, it will be assumed that claim 111 depends from claim 110.

Correction is required.

22. Claim 112 is indefinite in the recitation of “protein of claim 98, wherein said biological activity is enzymatic activity” for the following reasons. There is no antecedent basis for a biological activity in claim 98. For examination purposes, it will be assumed that claim 112 depends from claim 110.

Correction is required.

23. Claim 113 is indefinite in the recitation of “having an increased affinity for said macrophages, in comparison with the corresponding affinity of a naturally occurring lysosomal protein to said macrophages” for the following reasons. The term “a naturally occurring lysosomal protein” encompasses any naturally occurring lysosomal protein. Therefore, as written, claim does not require the comparison to be made with the affinity for macrophages of the corresponding protein lacking the glycosylation pattern present on the protein of claim 111 but it requires a comparison between the affinity of the protein of claim 111 for macrophages with the affinity for macrophages of any naturally occurring lysosomal protein. The basis for comparison is variable, thus making the determination as to whether prior art anticipates the claims impossible. A reference can be at the same time anticipatory and non-anticipatory depending on what is used as the basis for comparison. For example, prior art may meet the limitations recited if the naturally occurring lysosomal protein is a rat glucocerebrosidase but may not meet the limitations recited if the naturally occurring lysosomal protein is a mouse glucocerebrosidase. For examination purposes, it will be assumed that the claim reads “in comparison with the affinity for macrophages of the corresponding naturally occurring human lysosomal protein. Correction is required.

24. Claim 127 is indefinite in the recitation of “wherein said human lysosomal protein having at least one exposed mannose residue comprises a dominant fraction of said lysosomal protein, as measured by

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linkage analysis” for the following reasons. As written, the protein having at least one exposed mannose residue comprises a fraction of itself. In addition, while there is antecedent basis for a human lysosomal protein comprising at least one xylose residue and at least one exposed mannose residue, there is no antecedent basis for a human lysosomal protein having at least one exposed mannose residue.

Furthermore, the term “dominant fraction” is a relative term for which neither the specification nor the claim provide a standard to ascertain the requisite degree. For examination purposes, it will be assumed the claim is a duplicate of claim 115. Correction is required.

25. Claim 143 is indefinite in the recitation of “the human lysosomal protein of claim 142 which comprises an amino acid sequence as set forth in SEQ ID NO: 14” for the following reasons. Claim 142 as interpreted requires SEQ ID NO: 8, SEQ ID NO: 2 at the C terminus of SEQ ID NO: 8, and SEQ ID NO: 1 at the N-terminus of SEQ ID NO: 8. While SEQ ID NO: 14 comprises SEQ ID NO: 2 (amino acids 1-22 of SEQ ID NO: 14) and comprises SEQ ID NO: 1 (amino acids 520-526 of SEQ ID NO: 2), it does not comprise SEQ ID NO: 8. See attached alignment. Since the scope of claim 143 and the scope of claim 142 are not related, it is unclear as to how it further limits claim 142. For examination purposes, it will be assumed that claim 143 is an independent claim directed to the polypeptide of SEQ ID NO: 14. Correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

26. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

27. Claims 98-102, 104-108, 110-119, 122-128 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

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was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 98-102, 104-108, 110-119, 122-128 require (1) a genus of human lysosomal proteins having any function and structure wherein said proteins comprise sugar residues attached in a specific manner, and (2) a genus of human glucocerebrosidases having any structure wherein said proteins comprise sugar residues attached in a specific matter. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials”. As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

There is no actual structural and/or functional limitation with regard to the members of the genus of proteins claimed. While the specification in the instant application discloses the structure of a single species of the claimed genus of human lysosomal proteins, i.e. the polypeptide of SEQ ID NO: 8, it provides no clue as to the structural elements required in any human lysosomal protein or any human

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glucocerebrosidase, nor does it teach which structural elements of the polypeptide of SEQ ID NO: 8 are required in any human lysosomal protein or any human glucocerebrosidase.

The claim encompasses a large genus of proteins which is structurally and functionally unrelated. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of human lysosomal proteins recited in the claim, and there is no information as to a correlation between structure and being a human lysosomal protein, or a correlation between structure and glucocerebrosidase activity. No correlation between the structure of the polypeptide of SEQ ID NO: 8 and any naturally-occurring human glucocerebrosidase has been provided either. Furthermore, while one could argue that SEQ ID NO: 8 is representative of the structure of all the members of the genus of glucocerebrosidases encompassed by the claims, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in enzymatic function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teach that one conservative amino acid substitution transforms a  $\beta$ -ketoacyl synthase into a malonyl decarboxylase and completely eliminates  $\beta$ -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teach that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes to a polypeptide may result in changes affecting function, and no additional information correlating structure with glucocerebrosidase activity, or correlating structure with being a human lysosomal protein has been provided, one cannot reasonably conclude that SEQ ID NO: 8 is representative of the structure of all human lysosomal proteins as claimed.

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Due to the fact that the specification only discloses a single species of the genus, i.e. the polypeptide of SEQ ID NO: 8, and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

28. Claims 98-102, 104-108, 110-119, 122-128 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 8 having a plant glycosylation pattern, and a pharmaceutical composition comprising said polypeptide, does not reasonably provide enablement for (1) any human lysosomal protein having a plant glycosylation pattern or any human glucocerebrosidase having a plant glycosylation pattern, or (2) any pharmaceutical composition comprising the proteins of (1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

***The breadth of the claims.*** Claims 98-102, 104-108, 110-119, 122-128 are so broad as to encompass any human lysosomal protein or any human glucocerebrosidase. The enablement provided is not commensurate in scope with the claim due to the extremely large number of proteins of unknown

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structure and/or function encompassed by the claim. In the instant case, the specification enables a single species, i.e., the polypeptide of SEQ ID NO: 8.

***The amount of direction or guidance presented and the existence of working examples.*** The specification discloses the amino acid sequence of a single protein as a working example (SEQ ID NO: 8). However, the specification fails to provide any clue as to the structural elements required in any human lysosomal protein or any human protein having glucocerebrosidase activity, or which are the structural elements in the polypeptide of SEQ ID NO: 8 which are essential for any protein to be a human lysosomal protein or a human glucocerebrosidase. No correlation between structure and function has been presented. There is no information or guidance as to which amino acid residues in the polypeptide of SEQ ID NO: 8 can be modified and which ones are to be conserved to create a variant displaying the same activity as that of the polypeptide of SEQ ID NO: 8.

***The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art.*** The amino acid sequence of a polypeptide determines its structural and functional properties. While the art discloses some human lysosomal proteins and a human glucocerebrosidase, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any human glucocerebrosidase or lysosomal protein. In addition, the art does not provide any teaching or guidance as to the extent of structural variability among all human glucocerebrosidases or how the structure of those known human lysosomal proteins correlate with any human lysosomal protein. The art clearly teaches that modification of a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are tolerant of modification and which ones are conserved is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New

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York, page 247) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

***The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.*** While methods of generating or isolating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all human lysosomal polypeptides or all human glucocerebrosidases. In the absence of (1) a rational and predictable scheme for isolating human lysosomal proteins or glucocerebrosidases, and/or (2) a correlation between structure and being a human lysosomal protein or a correlation between structure and glucocerebrosidase activity, one of skill in the art would have to test an extremely large number of human proteins and determine which ones have the desired characteristics.

Therefore, taking into consideration the extremely broad scope of the claim, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and the desired function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

*Claim Rejections - 35 USC § 102*

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

30. Claims 98-102, 110-119, 127, 128 are rejected under 35 U.S.C. 102(b) as being anticipated by Garger et al. (U.S. Publication 2002/0088224, published 7/4/2001; application No. 09/993059 filed on 11/13/2001). Claims 98-102, 110-119, 127-128 are directed in part to (1) a human glucocerebrosidase which comprises an exposed mannose residue, a fucose residue having an alpha (1-3) glycosidic bond and a xylose residue, (2) a plant cell preparation comprising the human glucocerebrosidase of (1), and pharmaceutical compositions comprising the human glucocerebrosidase of (1) or the plant cell preparation of (2). See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation. Garger et al. teach the recombinant production of human glucocerebrosidase in transgenic tobacco plants (Examples 1-7; called rGCB). Garger et al. also teach the enzymatic removal of sialic acid, galactose, and N-acetylglucosamine residues to prepare glucocerebrosidase for therapy (page 14, paragraph [0164], lines 12-15; page 1, paragraph [0006], lines 18-26) and that their rGCB co migrates with the mannose-terminal therapeutic glycoform. Garger et al. teach that one of the uses for the recombinant rGCB produced in plants is for therapy (page 6, paragraph [0045]). As known in the art, xylose residues and core alpha (1-3) fucose residues are added to proteins in plants during the glycosylation process. Garger et al. teach that the rGCB produced in transgenic tobacco plants has xylose and fucose residues (page 13, paragraph [0125], last two sentences). Also, as known in the art, removal of sialic acid, galactose, and N-acetylglucosamine residues would result in mannose residues being exposed. The instant reference further teaches the purification of the rGCB (Example 5). Therefore, the teachings of Garger et al. anticipate the instant claims as written.

*Claim Rejections - 35 USC § 103*

31. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

32. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(c), (f) or (g) prior art under 35 U.S.C. 103(a).

33. Claims 104-107, 122-125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garger et al. (U.S. Publication 2002/0088224, published 7/4/2001; application No. 09/993059 filed on 11/13/2001) in view of Boller et al. (U.S. Patent No. 6054637, issued 4/25/2000) and further in view of Stomp et al. (U.S. Patent No. 6815184, application 09/915873 filed on 7/26/2001). The teachings of Garger et al. have been discussed above. Garger et al. do not teach the human glucocerebrosidase linked at the N-terminus to an endoplasmic reticulum signal peptide and linked at the C-terminus to the basic tobacco chitinase A gene vacuolar targeting signal peptide. Boller et al. teach that one of the advantages in directing proteins to the vacuole is due to the fact that vacuoles constitute the largest storage compartment in plants for dissolved substances (column 2, line 57-column 3, line 1). Boller et al. teach several signal peptides for vacuolar sorting including a tobacco chitinase gene vacuolar targeting signal peptide which comprises SEQ ID NO: 2 (SEQ ID NO: 29 in that patent). Boller et al. disclose adding the

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DNA encoding the vacuolar targeting signal peptide at the 3' end of any desirable expressible DNA. As such, Boller et al. teach adding the vacuolar signal peptide to the C-terminus of any desired protein (column 8, lines 38-52). Stomp et al. teach an ER signal from the *Arabidopsis thaliana* endochitinase gene which comprises all of SEQ ID NO: 1 except for the last amino acid (column 13, lines 5-26; SEQ ID NO: 8 in that patent), and that addition of such signal as well as other known ER signals is often used to target the desired protein to the ER. Stomp et al. teach that the ER signal from the *Arabidopsis thaliana* endochitinase gene is found at the N-terminus of the *Arabidopsis thaliana* endochitinase gene (amino acids 14-34 of the endochitinase disclosed in GenBank accession No. BAA82823). Neither Boller et al. nor Stomp et al. teach the human glucocerebrosidase of Garger et al.

Claims 104-107 and 122-125 are directed in part to the human glucocerebrosidase of claim 98 or the plant cell preparation of claim 115 described above, wherein said the human glucocerebrosidase is linked at the N-terminus to an endoplasmic reticulum signal peptide and at the C-terminus to a vacuolar targeting signal peptide comprising SEQ ID NO: 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a fusion protein comprising an endoplasmic reticulum signal peptide linked to the N-terminus of the human glucocerebrosidase of Garger et al. and a vacuolar signal peptide comprising SEQ ID NO: 2 at the C-terminus of the human glucocerebrosidase of Garger et al. A person of ordinary skill in the art is motivated to construct such fusion protein because (1) Boller et al. teach the advantages of directing a desired protein to the vacuole of a plant, and (2) the human glucocerebrosidase of Garger et al. requires glycosylation. As known in the art and taught by Garger et al., the initial steps in the glycosylation process take place in the endoplasmic reticulum (page 3, paragraph [0025]). Therefore, adding an ER signal to the human glucocerebrosidase of Garger et al. would direct this protein to the ER for glycosylation. One of ordinary skill in the art has a reasonable expectation of success at making the fusion protein of Garger et al., Boller et al. and Stomp et al. since Boller et al. and Stomp et al. teach

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fusion proteins comprising said signal peptides, and the use of fusion proteins comprising the desired protein linked to heterologous signal peptides is well known and widely practiced in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

### ***Double Patenting***

34. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

35. Claims 98-102, 104-113, 115-120, 122-128 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 27-30, 32, 34-39, 41-44, 46-49, 51-52, 55-61 of copending Application No. 11/790991. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

36. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research

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agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

37. Claims 114, 142-144 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39, 45 of copending Application No. 11/790991. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Claim 114 is directed to a pharmaceutical composition comprising a human lysosomal protein having one mannose residue and at least one fucose residue having an alpha(1-3) glycosidic bond. Claims 142-144 are directed to the protein of SEQ ID NO: 8 further comprising the signal peptide of SEQ ID NO: 1 at the N-terminus of SEQ ID NO: 8 and the vacuolar targeting signal peptide of SEQ ID NO: 2 at the C-terminus of SEQ ID NO: 8. See Claim Rejections under SEQ ID NO: 112 second paragraph, for claim interpretation. Claims 39 and 45 of copending application No. 11/790991 are directed to a human lysosomal protein comprising SEQ ID NO: 8 comprising one xylose residue and one exposed mannose residue, and a pharmaceutical composition comprising said human lysosomal protein. The specification of copending application No. 11/790991 teaches as a preferred embodiment of the invention, the polypeptide of SEQ ID NO: 14, which is the protein of SEQ ID NO: 8 further comprising the signal peptide of SEQ ID NO: 1 at the N-terminus of SEQ ID NO: 8 and the vacuolar targeting signal peptide of SEQ ID NO: 2 at the C-terminus of SEQ ID NO: 8. The specification also discloses as a preferred embodiment of the invention, the plant-glycosylated protein of SEQ ID NO: 14, wherein said protein comprises exposed mannose residues, a xylose residue and a fucose residue. Therefore, in view of the preferred embodiments disclosed in the specification of copending Application No. 11/790991, the invention of claims 114, 142-144 are deemed an obvious variation of the invention of claims 39, 45 of copending Application No. 11/790991.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

38. No claim is in condition for allowance.

39. The cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site ([www.uspto.gov](http://www.uspto.gov)), from the Office of Public Records and from commercial sources.

40. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

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